

CLAIMS:

1. A peptide consisting essentially of at least four sequential amino acids from a negative regulatory region which maps to residues 361-383 of p53, said peptide not being a subfragment of human p53, wherein said peptide activates DNA binding of wild-type p53 or a p53 mutant containing a single amino acid substitution, said mutant selected from the group consisting of p53-ser²³⁹, p53-his²⁷³, p53-gln²⁴⁸, p53-trp²⁸², and p53-cys²⁷³, in a p53 DNA binding assay.
2. The peptide according to claim 1, said peptide containing residues 363-373, 368-380, 373-383, 371-383, 363-382, 378-382, 367-386, 363-386, 362-386 or 360-386 of human p53.
3. The peptide according to claim 1, said peptide containing residues 363-370, 368-373, 368-372, 369-373, 370-375, or 370-374 of human p53.
4. The peptide according to claim 1, wherein at least one of said at least four amino acids is substituted by the corresponding residue from a non-human p53 sequence.
5. The peptide according to claim 1, said peptide containing both L-amino acids and D-amino acids.
6. The peptide according to claim 5, wherein the N-terminal amino acid of the peptide is a D-amino acid.
7. The peptide according to claim 5, wherein the C-terminal amino acid is a D-amino acid.
8. The peptide according to claim 1, wherein said at least four sequential amino acids are D-amino acids which map to the negative regulatory region (represented by residues 361-383 of human p53) in a reverse sequence orientation, relative to the wild-type sequence.
9. The peptide according to claim 1, wherein said peptide is cyclic.
10. The peptide according to claim 1, wherein one or more natural amino acids are substituted by unnatural amino acids of similar chemical structure.
11. The peptide according to claim 10, wherein the natural amino acid is a serine and the unnatural amino acid is an isoserine.
12. A method for identifying a peptidomimetic which activates DNA binding of wild-type p53, wherein said method comprises selecting a non-peptidyl compound having a similar

structure to a peptide according to any one of claims 1-11, and determining the ability of said compound to stimulate DNA binding in a p53 DNA binding assay.

13. A method for identifying a peptidomimetic which activates DNA binding of wild-type p53, wherein said method comprises selecting a compound wherein part of a peptide according to any one of claims 1-11 is substituted by a non-peptidyl moiety with similar structure, and determining the ability of said compound to stimulate DNA binding in a p53 DNA binding assay.

14. A peptidomimetic identified according to claim 12, said peptidomimetic having the biological activity of a peptide consisting essentially of at least four sequential amino acids from a negative regulatory region which maps to residues 361-383 of p53.

15. A peptidomimetic identified according to claim 13, said peptidomimetic having the biological activity of a peptide consisting essentially of at least four sequential amino acids from a negative regulatory region which maps to residues 361-383 of p53.

16. A peptidomimetic consisting essentially of at least four sequential amino acids from a negative regulatory region which maps to residues 361-383 of p53, said peptidomimetic having the biological activity of the peptide according to claim 1.

17. A peptidomimetic consisting essentially of at least four sequential amino acids from a negative regulatory region which maps to residues 361-383 of p53, wherein one or more peptide bonds are replaced by a reduced isostere pseudopeptide bond, said peptidomimetic having the biological activity of the peptide according to claim 1.

18. A peptidomimetic consisting essentially of at least four sequential amino acids from a negative regulatory region which maps to residues 361-383 of p53, wherein one or more peptide bonds are replaced by a retro-inverso pseudopeptide bond, said peptidomimetic having the biological activity of the peptide according to claim 1.

19. A peptidomimetic consisting essentially of at least four sequential amino acids from a negative regulatory region which maps to residues 361-383 of p53, wherein one or more amino acid residues are replaced by the corresponding N-substituted glycine, said peptidomimetic having the biological activity of the peptide according to claim 1.

20. A method for identifying p53 mutants whose ability to bind DNA may be activated by peptides or peptidomimetics corresponding to all or a portion of the negative regulatory region which maps to residues 361-383 of p53, comprising mixing a sample

containing a p53 mutant protein with a peptide or peptidomimetic according to any one of claims 1-11 or 16-19, and subjecting the mixture to a DNA binding assay which measures DNA binding of p53 or mutants thereof, wherein DNA binding of said p53 mutants is activated by said peptide or peptidomimetic relative to DNA binding in the absence of said peptide or peptidomimetic.

21. The method of claim 20, wherein the DNA binding assay measures binding to a double-stranded DNA molecule comprising 5'-TGGCATGTCATGGCATGTCA-3'.

22. A pharmaceutical composition comprising a peptide or peptidomimetic according to any one of claims 1-11 or 16-19 in a pharmaceutically acceptable carrier.

Surf A22
23. A method of treating an individual for a condition selected from the group consisting of exposure to DNA damaging agents, abnormal cell proliferation characteristic of psoriasis, atherosclerosis, cancer, and arterial restenosis, undesirable immune response accompanying rejection of a transplant and an autoimmune disease, comprising administering to the patient a pharmaceutical composition of claim 22.

24. A method for treating a patient having a tumor expressing a p53 mutant whose ability to bind DNA may be activated by peptides, modified peptides or peptidomimetics corresponding to all or a portion of the negative regulatory region which maps to residues 361-383 of p53, said method comprising administering to said patient a pharmaceutical composition according to claim 22.

25. The method of claim 24, wherein said p53 mutant is selected from the group consisting of p53-ser²³⁹, p53-his²⁷³, p53-gln²⁴⁸, p53-trp²⁸², and p53-cys²⁷³.

26. The method of claim 24, wherein said ability to bind DNA is determined by mixing a sample from the tumor of said patient containing a p53 mutant protein with a peptide, modified peptide or peptidomimetic corresponding to all or a portion of said negative regulatory region, and measuring the ability of the mixture to bind DNA in a p53 DNA binding assay.